DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103792/5311

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING
COMMITMENTS

Genentech, Inc.
Attention: Dhushy Thambipillai
Regulatory Program Management
1 DNA Way, MS 241B
South San Francisco, CA 94080-4990

Dear Ms. Thambipillai:

Please refer to your Supplemental Biologics License Application (sBLA), dated November 25, 2013, received November 26, 2013, submitted under section 351(a) of the Public Health Service Act for Herceptin® (trastuzumab).

We acknowledge receipt of your amendment dated February 21, 2014.

This Prior Approval supplemental biologics application provides for: 1) the efficacy and safety results from the protocol-specified preplanned final OS analysis of studies NSABP B-31 and NCCTG N9831 in fulfillment of PMCs 1 and 3 from BLA 103792/5150 and 2) update the USPI for Herceptin to include information on Herceptin administered concurrently with the taxane component of adjuvant chemotherapy in the treatment of patients with HER2 positive EBC. The analyses included in the Final Clinical Study Report – Joint Analysis of Studies NSABP B-31 and NCCTG N9831 are:

- ☐ Overall survival (OS; final analysis based on 707 deaths [710 planned])
- ☐ Disease Free Survival (DFS, updated analysis)
- ☐ Cardiac safety (final, comprehensive analysis)

APPROVAL & LABELING

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling

[21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling text for the package insert and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING COMMITMENTS

We have received your submission dated November 25, 2013, containing the final reports for the following postmarketing commitments listed in the November 16, 2006, approval letter for BLA 103792/5150.

1. To provide a final study report at the time of the final analysis of overall survival (analysis based on 710 deaths) in accordance with the statistical analysis plan of April 2005 for integrated analysis of Studies NSABP B31 and NCCTG N9831. The final study report should include the primary datasets and programs for generation of analyses and all subset analyses for the final analysis of overall survival and an updated analysis of disease-free survival, including exploratory analyses in subgroups based on the timing and type of hormonal treatment administered to patients.

3. To provide interim cardiac safety updates on an annual basis beginning on 30 September 2006, as the first cutoff date and ending with a final comprehensive cardiac safety analysis report submitted by 30 September 2012. Each annual cardiac safety update will include a detailed narrative summary of each new clinical event with associated radiologic reports and laboratory findings for all

patients enrolled as of the termination of study enrollment in April 2005. The first annual cardiac safety update will be submitted by 28 April 2007. The final comprehensive cardiac safety analysis will be included in the final study report based on 710 deaths. In addition, the final comprehensive study report will contain primary datasets for the ITT population and summary analyses that include, but are not limited to, the analyses described in the statistical analysis plan of April 2005 for integrated analysis of Studies NSABP B31 and NCCTG N9831.

We have reviewed your submission and conclude that the above commitments are fulfilled.

We remind you that there are postmarketing requirements and postmarketing commitments still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Amy Tilley, Regulatory Project Manager, at (301) 796-3994 or amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, M.D.
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMNA IBRAHIM
03/07/2014